Kidney International (2009) **76**, 1017–1018. doi:10.1038/ki.2009.395

Effects of dopamine on graft function after kidney transplantation

Schnuelle *et al.*, *JAMA* 2009; **302**: 1067–1075

Early but growing preclinical and clinical literature suggests that donor pretreatment with certain agents may enhance outcomes following transplantation. These include methylprednisolone, antilymphocyte globulin, atorvastatin, and dopamine. The investigators of this study previously demonstrated that dopamine and norepinephrine administration to the donor was associated with fewer episodes of acute rejection and superior long-term graft survival. A new randomized trial by Schnuelle *et al.* was undertaken to more firmly establish cause and effect. This open-label, multicenter trial randomized heart-beating donors to receive or to not receive dopamine as a continuous infusion begun after confirmation of brain death, continued until cross-clamping, and titrated on the basis of hemodynamics. The two groups were similar with respect to all characteristics with one exception. The group randomized to dopamine had slightly less concomitant treatment with norepinephrine. Donor dopamine treatment significantly reduced use of dialysis after transplantation. Among recipients of kidneys from donors treated with dopamine, 66% did not require dialysis, 9% required only one session of dialysis, and 25% required multiple sessions of dialysis. Among recipients of kidneys from donors who were not treated with dopamine, 59% did not require dialysis, 5% required only one session of dialysis, and 35% required multiple sessions of dialysis. Among recipients of kidneys from donors treated with dopamine, 85%, 83%, and 81% of the kidneys were functioning at 1, 2, and 3 years, respectively. Among recipients of kidneys from donors not treated with dopamine, 87%, 81%, and 75% of the kidneys were functioning at 1, 2, and 3 years, respectively. Interestingly, the benefit appeared strongest among recipients who received kidneys with the longest cold ischemia time.

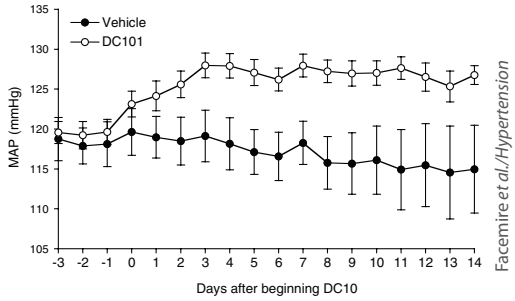
This trial demonstrated a 15% reduction in post-transplantation dialysis. The possibility that a type II error occurred must be considered, because the report does not state whether power was available to show a difference. Further study will be necessary to parse this out.

Lynda Szczech

Vascular endothelial growth factor and blood pressure regulation

Facemire *et al.*, *Hypertension* 2009; **54**: 652–658; doi:10.1161/HYPERTENSIONAHA.109.129973

Vascular endothelial growth factor (VEGF) induces angiogenesis but also regulates vascular permeability, endothelial-cell survival, and hematopoiesis. The major receptors for VEGF are two related tyrosine kinases, VEGFR1 (Flt-1) and VEGFR2 (Flk-1), the latter mediating its angiogenic, mitogenic, and permeability-enhancing effects. As stimulation of angiogenesis by VEGF is critical in the growth and spread of various cancers, antibodies and small molecules targeting this factor and its associated signaling pathways



Blood pressure in mice treated with anti-VEGFR2 monoclonal antibody (DC101) or vehicle.

are currently used in the treatment of a variety of human malignancies. Interestingly, along with its actions on blood vessel growth and permeability, VEGF also has systemic hemodynamic effects. For example, acute infusions of VEGF cause vasodilation and hypotension, likely mediated by VEGFR2 and stimulation of nitric oxide (NO) synthesis and/or vasodilator prostanoids. Further, hypertension has emerged as one of the most common adverse effects of VEGF inhibitors in patients treated for malignancies. To elucidate the molecular mechanisms underlying the effects of VEGF on the systemic circulation and blood pressure, Facemire *et al.* administered a specific monoclonal antibody against VEGFR2 to normal mice and found that it caused a rapid and sustained increase in blood pressure of about 10 mm Hg (Figure). The increase in blood pressure was associated with a significant reduction in renal renin mRNA expression and in urinary excretion of aldosterone. The anti-VEGFR2 antibody also caused a marked decrease in the expression of endothelial and neuronal NO synthases in the kidney. Administration of the inhibitor of NO production N_{ω}-nitro-L-arginine methyl ester (L-NAME) abolished the difference in blood pressure between the control and anti-VEGFR2-treated animals. These data thus suggest that VEGF, acting via VEGFR2, plays a critical role in the control of normal blood pressure by promoting NO synthase expression and NO activity. Interfering with this pathway is likely to be a mechanism underlying hypertension caused by antiangiogenic agents targeting VEGF.

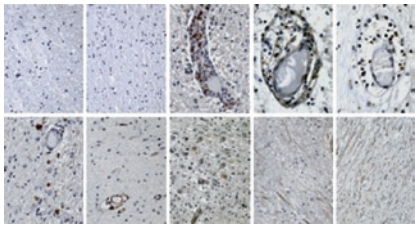
Juan Oliver

Exploring novel aspects of the RAS in cellular immunology

Stegbauer *et al.*, *Proc Natl Acad Sci USA* 2009; **106**: 14942–14947; doi:10.1073/pnas.0903602106

Platten *et al.*, *Proc Natl Acad Sci USA* 2009; **106**: 14948–14953; doi:10.1073/pnas.0903958106

In immunological diseases, including systemic lupus erythematosus, examination of the RAS has been mostly restricted to the potential of the RAS to modify the response to proinflammatory cytokines. Now, two articles explore novel aspects of the RAS in cellular immunology. Stegbauer *et al.* studied the role of the RAS in myelin-oligodendrocyte glycoprotein-induced experimental



Expression of AT1R in MS plaques.

autoimmune encephalomyelitis (MOG-EAE), a model mimicking many aspects of multiple sclerosis (MS). Quantitative real-time PCR analyses showed an upregulation of renin, angiotensin-converting enzyme, and angiotensin II type 1 receptor (AT1R) in the inflamed spinal cord and the immune system, including antigen-presenting cells (APCs). Treatment with the renin inhibitor aliskiren or the angiotensin II-converting enzyme (ACE) inhibitor enalapril, as well as preventive or therapeutic application of the AT1R antagonist losartan, resulted in a significantly ameliorated course of MOG-EAE. Blockade of AT1R did not directly impact T-cell responses but significantly reduced the numbers of $CD11b^+$ or $CD11c^+$ APCs in immune organs and in the inflamed spinal cord. Additionally, AT1R blockade impaired the expression of CCL2, CCL3, and CXCL10, and reduced CCL2-induced APC migration. These findings suggest a pivotal role of the RAS in autoimmune inflammation of the central nervous system, a conclusion supported by another study. Here, Platten *et al.* show that the RAS also plays a major role in T cells during autoimmunity, exemplified by MS and its animal model, experimental autoimmune encephalomyelitis (EAE). Using proteomics, they observed that the renin–angiotensin–aldosterone system is upregulated in brain lesions of MS. By further analyzing the T-cell response, Platten *et al.* found that the angiotensin receptor AT1R (Figure) was induced in myelin-specific $CD4^+$ T cells and monocytes during autoimmune neuroinflammation. Blocking angiotensin II production with ACE inhibitors or inhibiting angiotensin II signaling with AT1R blockers suppressed autoreactive TH1 and TH17 cells and promoted antigen-specific $CD4^+FoxP3^+$ regulatory T cells with inhibition of the canonical nuclear factor-κB1 transcription factor complex and activation of the alternative nuclear factor-κB2 pathway. Treatment with ACE inhibitors reversed the neurological sequelae of EAE. These exciting studies imply a direct role of the RAS in regulating T-cell responses and thereby influencing the outcome of immunological diseases.

The authors of both studies propose that modulation of the RAS may represent an attractive supplemental therapeutic strategy for application to human autoimmune diseases.

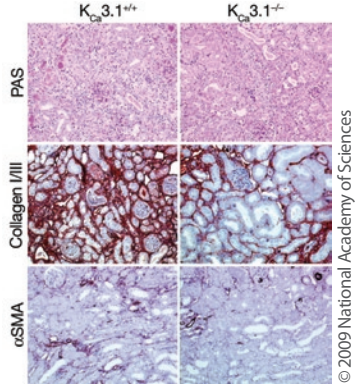
Detlef Schlöndorff

Involvement of potassium channels in renal fibrosis

Grgic *et al.*, *Proc Natl Acad Sci USA* 2009; **106**: 14518–14523; doi:10.1073/pnas.0903458106

Progressive renal fibrosis is a characteristic of many kidney diseases that result in end-stage renal failure. In the diseased kidney, some renal fibroblasts derive from epithelial cells and some from the bone marrow, but since resident interstitial fibroblasts likely represent the major source of newly generated fibroblasts, inhibition of their proliferation may provide a therapeutic strategy. Indeed, several molecules with antifibrotic properties, such as bone morphogenic protein 7, hepatocyte growth factor, and pirfenidone, have been proposed as potential therapies. A variety of studies suggest that fibroblast proliferation in the kidney is due to locally secreted fibrogenic chemokines, including transforming growth factor-β_1, platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and basic fibroblast growth factor (bFGF). However, recent work suggests that ion channels play a role in cell proliferation by enhancing intracellular Ca^{2+} signaling and affecting cell-cycle progression. In this regard, Ca^{2+}-permeable cation channels and Ca^{2+}-activated K^+ channels (K_{Ca}) seem to be critical. Whereas the former directly mediate Ca^{2+} inflow, the latter regulate membrane potential and thus provide the driving force for Ca^{2+} entry. In particular, the intermediate-conductance K_{Ca} ($K_{Ca}3.1$) channel has been shown to promote mitogenesis in several tissues and cell lines. Interestingly, mitogens such as bFGF, PDGF, and vascular endothelial growth factor (VEGF) upregulate $K_{Ca}3.1$, and pharmacological inhibition or knock-down of $K_{Ca}3.1$ suppresses mitogen-driven cell proliferation. Grgic *et al.* postulated that $K_{Ca}3.1$ channels promote renal fibroblast proliferation and development of renal tubulointerstitial fibrosis. They found that mitogenic stimulation upregulated $K_{Ca}3.1$ in murine renal fibroblasts via a MEK-dependent mechanism, and that selective blockade of $K_{Ca}3.1$ inhibited fibroblast proliferation by G_0/G_1 arrest. *In vivo*, renal fibrosis induced by unilateral ureteral obstruction (UUO) was associated with a robust upregulation of $K_{Ca}3.1$ in the kidney. In addition, mice lacking $K_{Ca}3.1$ ($K_{Ca}3.1^{-/-}$) showed a significant reduction in fibrotic marker expression, chronic tubulointerstitial damage, collagen deposition, and α-smooth muscle actin-positive (αSMA) cells in kidneys after UUO (Figure). Similarly, treatment with the selective $K_{Ca}3.1$ blocker TRAM-34 also attenuated progression of UUO. Thus, these results demonstrate that $K_{Ca}3.1$ is involved in renal fibroblast proliferation and fibrogenesis and suggest that this ion channel may be a therapeutic target for treatment of fibrotic kidney disease.

Juan Oliver



Genetic deficiency of $K_{Ca}3.1$ attenuates progression of renal fibrosis after UUO in mice. Periodic acid-Schiff, collagen I/III, and αSMA staining from UUO kidneys of wild-type ($K_{Ca}3.1^{+/+}$) and $K_{Ca}3.1$ knockout ($K_{Ca}3.1^{-/-}$) mice.